Search Strategy

FILE 'USPATFULL' ENTERED AT 14:13:42 ON 28 JUL 2002

		E	GAILLAC DAVID/IN
		E	KOEHL M/IN
L1	1	S	E4
		E	KAMEYAMA SHOJU/IN
L2	3	S	E2-E4
L3	569	S	(VIRUS-INACTIVAT?)
L4	115	S	L3 AND (TNBP OR TRI-N-BUTYL PHOSPHATE)
L5	84	S	L4 AND (TWEEN 80)
L6	24	S	L5 AND (TNBP/CLM OR TRI-N-BUTYL PHOSPHATE/CLM)
L7	8	S	L6 AND TWEEN/CLM

FILE 'WPIDS' ENTERED AT 14:32:58 ON 28 JUL 2002

		E	GAILLAC D/IN
L8	2	S	E3
		E	KAMEYAMA SHOJU/IN
L9	63	S	E2
L10	1	S	L9 AND VIRUS-INACTIVAT?
L11	211	S	(VIRUS-INACTIVAT?)
L12	13	S	L11 AND (TNBP OR TRI-N-BUTYL PHOSPHATE)
L13	3	S	L12 AND TWEEN

FILE 'MEDLINE' ENTERED AT 14:36:22 ON 28 JUL 2002

		E	GAILLAC D/AU
L14	1	S	E3
		E	KOEHL M/AU
L15	13	S	E3
L16	617	S	(VIRUS-INACTIVAT?)
L17	20	S	L16 AND (TNBP OR TRI-N-BUTYL PHOSPHATE)
L18	5	S	L17 AND TWEEN

L2 ANSWER 1 OF 3 USPATFULL
92:80898 Production method for protein-containing composition.
Kameyama, Shoju, Hirakata, Japan
Miyano, Kenmi, Hirakata, Japan
Hashimoto, Motonori, Hirakata, Japan
Takechi, Kazuo, Hirakata, Japan
Ohmura, Takao, Hirakata, Japan
Hirao, Yutaka, Hirakata, Japan
Uemura, Yahiro, Hirakata, Japan
Yokoyama, Kazumasa, Hirakata, Japan
The Green Cross Corporation, Osaka, Japan (non-U.S. corporation)
US 5151499 19920929
APPLICATION: US 1990-464077 19900112 (7)
PRIORITY: JP 1989-6736 19890113
JP 1989-308466 19891127
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method of producing a virus-inactivated protein-containing composition from a protein-containing composition which may be contaminated with virus. The method according to the present invention permits production of pharmaceutically safer virus-inactivated protein preparations without spoiling the protein activity.

CLM What is claimed is:
1. A method for preparing a virus-inactivated protein-containing composition from a protein-containing composition which may be contaminated with virus and which composition is treated in a liquid state and in a dry state, comprising the steps of (a) contacting the protein-containing composition in a liquid state with a trialkyl phosphate, and (b) heat-treating the protein-containing composition in a dry state to the extent that a non-envelope virus contained therein is inactivated, wherein the steps (a) and (b) are performed in any order.

2. A method as in claim (1), wherein the protein is derived from plasma.

3. A method as in claim (1), wherein the heat-treating step (b) follows contacting step (a).

4. A method as in claim (1), wherein the trialkyl phosphate is tri-(n-butyl) phosphate.

5. A method as in claim (1), wherein a trialkyl phosphate is used in an amount of from 0.01 to 10 (w/v) %.

6. A method as in claim (1), wherein the protein-containing liquid composition is brought into contact with a trialkyl phosphate in the presence of a surfactant.

7. A method as in claim (1), wherein the heat treatment is conducted at 30.degree. C. to 100.degree. C. for 3 to 200 hours.

8. A method as in claim (1), wherein the protein is at least one species selected from among the group consisting of blood coagulation factor VIII, blood coagulation factor IX, thrombin, fibrinogen and fibronectin.

9. A method for preparing a virus-inactivated protein-containing composition from a protein-containing composition which may be contaminated with virus, comprising the steps of: (a) contacting a protein-containing liquid composition with a trialkyl phosphate; (b)

removing the trialkyl phosphate and recovering the protein from the thus treated protein-containing liquid composition; (c) lyophilizing the recovered protein to obtain a dry protein-containing composition; and (d) heat-treating the dry protein-containing composition to the extent that a non-envelope virus contained therein is inactivated.

10. A method as in claim 1, wherein said virus is echo virus.

11. A method as in claim 9, wherein said virus is echo virus.

12. A method for preparing a virus-inactivated protein-containing composition from a protein-containing composition which may be contaminated with virus, comprising the steps of: (a) contacting a protein-containing liquid composition with a trialkyl phosphate; (b) removing the trialkyl phosphate and recovering the protein from the thus treated protein-containing liquid composition; (c) lyophilizing the recovered protein to obtain a dry protein-containing composition; and (d) heat-treating the dry protein-containing composition to the extent that a non-envelope virus contained therein is inactivated, wherein the protein is at least one species selected from the group consisting of blood coagulation factor VIII, blood coagulation factor IX, thrombin and fibrinogen.

13. A method as in claim 12, wherein said virus is echo virus.

14. A method as in claim 12, wherein the trialkyl phosphate treatment is carried out at from -5.degree. C. to 70.degree. C. for more than 30 minutes.

15. A method as in claim 12, wherein the heat treatment is conducted at 30.degree. C. to 100.degree. C. for 3 to 200 hours.

16. A method as in claim 12, wherein the heat treatment is conducted at 55.degree. C. to 75.degree. C. for 10 to 100 hours.

L5 ANSWER 2 OF 84 USPATFULL
2002:133503 A METHOD FOR THE INACTIVATION OF NON-LIPID-COATED VIRUSES.
STADLER, MONIKA, SCHWECHAT, AUSTRIA
SCHWINN, HORST, MARBURG, GERMANY, FEDERAL REPUBLIC OF
JOSIC, DJURO, WIEN, AUSTRIA
GEHRINGER, WERNER, WIEN, AUSTRIA
BAL, FREDERIC, WIEN, AUSTRIA
US 2002068355 A1 20020606
APPLICATION: US 1995-501034 A1 19950928 (8)
PRIORITY: DE 1993-4303609 19930209
DE 1993-4318435 19930603
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method for the inactivation of viruses, in particular those having no lipid coats, in protein-containing compositions from blood, blood plasma or similar natural sources by treating said source, simultaneously or succesively, with an effective amount of dialkyl or trialkyl phosphates and optionally surfactants at an elevated temperature in the range of from 55.degree. C. to 67.degree. C. for five hours to 30 hours.

CLM What is claimed is:
1. A method for the inactivation of non-lipid-coated viruses in protein-containing compositions from blood, blood plasma or similar natural sources by treating said source, simultaneously or succesively, with an effective amount of dialkyl or trialkyl phosphates and

optionally surfactants at an elevated temperature in the range of from 60.degree. C. to 65.degree. C. for five hours to 30 hours.

2. The method according to claim 1, wherein the amount of said dialkyl or trialkyl phosphate is between 0.001% and 1%.

3. The method according to claim 1 and/or 2, wherein the duration of the heat treatment is at least 10 hours.

4. The method according to any of claims 1 to 3, wherein the protein is first enriched from said natural source by chromatographic or precipitation methods.

5. The method according to any of claims 1 to 4, wherein auxiliary substances, such as saccharose, sorbitol or short-chain neutral amino acids, are added prior to treatment with dialkyl or trialkyl phosphates with simultaneous treatment at elevated temperatures.

6. The method according to claim 5, wherein the concentration of saccharose is up to 200% by weight.

7. The method according to claim 5 and/or 6, wherein the amino acids glycine, lysine and/or arginine are employed.

8. The method accoring to any of claims 1 to 7, wherein treatment at elevated temperatures is performed without addition of calcium ions.

9. The method according to any of claims 1 to 8, wherein the treatment with said dialkyl or trialkyl phosphates with simultaneous heat treatment is followed by another chromatographic purification step.

10. The method according to any of claims 1 to 9, wherein the pH value in the treatment with dialkyl or trialkyl phosphates at elevated temperatures is from 6.0 to 8.5.

L5 ANSWER 23 OF 84 USPATFULL
2000:141889 Method of inactivating lipid-enveloped viruses.
Barrett, Noel, Klosterneuburg/Weidling, Austria
Kistner, Otfried, Vienna, Austria
Dorner, Friedrich, Vienna, Austria
Baxter Aktiengesellschaft, Vienna, Austria (non-U.S. corporation)
US 6136321 20001024
APPLICATION: US 1998-21146 19980210 (9)
PRIORITY: AT 1997-299 19970224
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention relates to a method of inactivating lipid-enveloped viruses by means of a non-ionic detergent, and the preparation of a vaccine containing the inactivated virus. The invention further relates to an inactivated virus which is characterized by its structural integrity, in particular the structural integrity of its enveloping proteins, as well as to the use of the inactivated virus for preparing a vaccine.

CLM What is claimed is:
1. A method of inactivating lipid-enveloped viruses comprising incubating (i) a whole lipid-enveloped virus having envelope proteins with (ii) a polysorbate selected from the group consisting of Tween.RTM. 80, Tween.RTM. 40, Tween.RTM. 20, and Tween.RTM. 60 at a concentration

between 1% to 20% for a period of time sufficient to inactivate said lipid-enveloped virus without disintegrating said whole virus, and without destroying the envelope proteins.

2. A method as set forth in claim 1, wherein said lipid-enveloped virus is selected from the group of retroviruses, flaviviruses, orthomyxoviruses, herpes viruses, paramyxoviruses, and arena viruses.

3. A method as set forth in claim 1, wherein said polysorbate is a stabilizing detergent.

4. A method as set forth in claim 1, wherein said whole virus is incubated with said polysorbate for at least 10 minutes.

5. A method as set forth in claim 1, further comprising removing said polysorbate after incubating.

6. A method as set forth in claim 5, wherein said polysorbate is removed by a chromatographic method.

7. A method as set forth in claim 5, wherein said polysorbate is removed by dialysis.

8. A method of preparing an inactivated whole virus, comprising providing an inactivated whole lipid-enveloped virus having envelope proteins, said virus having been inactivated by incubating a whole virus with a polysorbate selected from the group consisting of Tween.RTM. 80, Tween.RTM. 40, Tween.RTM. 20, and Tween.RTM. 60 at a concentration between 1% to 20% for a period of time sufficient to inactivate said virus without disintegrating said whole virus, and without destroying the envelope proteins, and admixing said inactivated lipid-enveloped virus with a physiologically acceptable carrier.

9. A method as set forth in claim 8, further comprising admixing said inactivated lipid-envloped virus with an adjuvant.

10. A virus preparation containing inactivated whole lipid-enveloped viruses, wherein the inactivated whole viruses comprise viral envelope proteins that are intact and possess native form and structure.

11. A virus preparation as set forth in claim 10, wherein said viral envelope proteins of said inactivated viruses have an immunogenicity and antigenicity that is not impaired compared to the respective native viruses that have not been inactivated.

12. A virus preparation as set forth in claim 10, further comprising a stabilizing agent.

13. A virus preparation as set forth in claim 12, wherein said stabilizing agent is a polysorbate selected from the group consisting of Tween.RTM. 80, Tween.RTM. 20, Tween.RTM. 60, and Tween.RTM. 40.

14. A method of inducing an immune response in a vertebrate comprising administering to the vertebrate a virus preparation containing inactivated whole lipid-enveloped viruses, wherein the inactivated whole lipid-enveloped viruses have been inactivated by incubating a whole lipid-enveloped virus with a polysorbate detergent selected from the group consisting of Tween.RTM. 80, Tween.RTM. 20, Tween.RTM. 60, and Tween.RTM. 40 at a concentration between 1% to 20% for a period of time sufficient to inactivate said virus without disintegrating said whole virus.

15. A virus preparation according to claim 13, wherein said polysorbate is contained at a concentration of between 0.05% and 0.5%.

16. A virus preparation according to claim 10, further comprising a physiologically acceptable carrier.

L7 ANSWER 8 OF 8 USPATFULL
92:36295 Virucidal euglobulin precipitation.
Tsav, Grace C., Walnut Creek, CA, United States
Miles Inc., Elkhart, IN, United States (U.S. corporation)
US 5110910 19920505
APPLICATION: US 1991-673991 19910325 (7)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A source for antibodies (both IgG and IgM types) is put into an aqueous solution which includes a virucidal agent under conditions sufficient to assure substantially complete dissolution of both the antibodies and the virucidal agent and virus inactivation. Then the pH, conductivity and antibody concentration of the solution are then changed to obtain conditions sufficient to assure the precipitation of substantially all antibodies while maintaining substantially all of the virucidal agent in the supernatant solution.

In preferred embodiments, using a TNBP/TWEEN virucidal agent, the original solution conductivity ranges from about 0.03 to 0.20 M MHO/CM, the pH ranges from about 4.75 to 4.85, and the protein concentration, when measured at A280, ranges from a reading of about 5 to 40. In the second precipitation step, the pH is changed to a range of about 6.0 to 7.5 and the conductivity is changed to a range of about 0.05 to 0.70 M MHO/CM to achieve an IgM precipitation ranging from about 30 to 80% by weight total protein.

CLM What is claimed is:
1. A method of preparing an antibody preparation comprising both IgM and IgG antibodies, the method comprising the steps of (a) mixing a source for the IgM and IgG antibodies in an aqueous solution in the presence of tri-n-butyl phosphate, the solution having a conductivity ranging from about 0.03 to 0.20 M MHO/CM, a pH ranging from about 4.75 to 4.85 and a protein concentration when measured at A280 ranging from about 5 to 40, to assure inactivation of substantially all viruses present; and (b) subjecting the solution to conditions sufficient to precipitate substantially all of the antibodies from the solution while maintaining substantially all of the tri -n-butyl phosphate in the supernate by simultaneously assuring a solution conductivity ranging from about 0.05 to 0.70 M MHO/CM, a pH ranging from about 6.0 to 7.5 and an amount of IgM antibody proportion in the precipitate ranging from about 20 to 80% by weight total protein precipitate.

2. The method of claim 1 wherein the source for the antibodies in Cohn Fraction III paste.

3. The method of claim 1 wherein the tri-n-butyl phosphate is water soluble at a pH ranging from about 4.75 to 7.5.

4. The method of claim 1 wherein at least 10% by weight of the source antibodies are precipitated in step (b) and at least 99% by weight of the original tri-n-butyl phosphate

remains in the supernate.

5. The method of claim 1 wherein the IgM antibodies precipitated in step (b) are at least 40% by weight of the total IgM antibodies in the source antibodies and at least 99.9% by weight of the original tri-n-butyl phosphate remains in the supernatant.

6. The method of claim 4 wherein the IgM antibody comprises at least about 30% by weight of the total antibody in the precipitate.

7. The method of claim 6 wherein the virucidal agent comprises Tween-80.

L8 ANSWER 1 OF 2 WPIDS (C) 2002 THOMSON DERWENT
AN 2000-549405 [50] WPIDS
DNC C2000-164085
TI Isolating virus particles from crude preparation, useful particularly for adenoviral gene therapy vectors, by adsorption on a fluidized bed and elution.
DC A96 B04 D16
IN GAILLAC, D; KOEHL, M
PA (TRGE) TRANSGENE SA
CYC 23
PI WO 2000050573 A1 20000831 (200050)* FR 42p
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE
W: AU CA JP US
AU 2000028118 A 20000914 (200063)
EP 1155120 A1 20011121 (200176) FR
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
ADT WO 2000050573 A1 WO 2000-FR430 20000221; AU 2000028118 A AU 2000-28118 20000221; EP 1155120 A1 EP 2000-906444 20000221, WO 2000-FR430 20000221
FDT AU 2000028118 A Based on WO 200050573; EP 1155120 A1 Based on WO 200050573
PRAI FR 1999-2167 19990222

AB WO 200050573 A UPAB: 20001010
NOVELTY - A crude preparation (A) containing viral particles (VP) is purified by at least one step of adsorption in a fluidized bed.
DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for a process for producing VP, useful in gene therapy, that includes purification as above.
USE - The method is particularly used to purify adenoviral vectors for gene therapy, particularly production of vaccines.
ADVANTAGE - Fluidized-bed adsorption is suitable for large scale purification of VP, e.g. 20 l batches of crude material can be treated. The method provides overall yield of VP about 80%, compare about 60% for packed-bed chromatography.
Dwg.0/0

L8 ANSWER 2 OF 2 WPIDS (C) 2002 THOMSON DERWENT
AN 2000-425187 [37] WPIDS
DNC C2000-128983
TI Inactivation of a viral preparation coated virus for therapeutic and prophylactic means, especially in gene therapy.
DC B04 D16
IN GAILLAC, D; KOEHL, M
PA (TRGE) TRANSGENE SA
CYC 28
PI EP 1016711 A1 20000705 (200037)* FR 18p
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
AU 9965358 A 20000622 (200037)
FR 2787465 A1 20000623 (200037)
JP 2000201673 A 20000725 (200040) 61p
CA 2292922 A1 20000621 (200044) FR
ADT EP 1016711 A1 EP 1999-403194 19991217; AU 9965358 A AU 1999-65358 19991220; FR 2787465 A1 FR 1998-16147 19981221; JP 2000201673 A JP 1999-363043 19991221; CA 2292922 A1 CA 1999-2292922 19991217
PRAI FR 1998-16147 19981221

AB EP 1016711 A UPAB: 20000807
NOVELTY - Inactivation of a virus coated in a viral preparation containing principally non coated virus is new and comprises introducing into the viral preparation an sufficient quantity of a solvent and leave to adjust

to a temperature of -5 - 50 deg. C, at a pH of 5-9 for a sufficient amount of time to significantly reduce the amount of viral preparation coated virus.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a process for the preparation of the viral preparation; and

(2) the viral preparation.

USE - The process is useful for inactivating virus' coated with a viral preparation susceptible to contamination by virus' coated, for therapeutic and prophylactic uses, especially in gene therapy for treating a genetic disorder e.g. hemophilia A or B, muscular dystrophy, Duchenne and Becker, diabetes, cystic fibrosis.

ADVANTAGE - No advantages stated in the specification.

Dwg.0/0

L10 ANSWER 1 OF 1 WPIDS (C) 2002 THOMSON DERWENT
AN 1990-218584 [29] WPIDS
DNN N1990-169634 DNC C1990-094387
TI Virus inactivation in protein compsns. - using tri alkyl phosphate in combination with heat treatment or protease inhibitor.
DC B04 P34
IN HASHIMOTO, M; HIRAO, Y; KAMEYAMA, S; MIYANO, K; OHMURA, T; TAKECHI, K; UEMURA, Y; YOKOYAMA, K
PA (GREC) GREEN CROSS CORP
CYC 11
PI EP 378208 A 19900718 (199029)* 17p
R: BE DE ES FR GB IT NL SE
CA 2007545 A 19900713 (199039)
JP 03218322 A 19910925 (199145)
US 5151499 A 19920929 (199242) 10p
EP 378208 B1 19940803 (199430) EN 21p
R: BE DE ES FR GB IT NL SE
DE 69011136 E 19940908 (199435)
ES 2057191 T3 19941016 (199442)
JP 09227405 A 19970902 (199745) 7p
JP 09227406 A 19970902 (199745) 9p
JP 2681406 B2 19971126 (199801) 9p
JP 2965069 B2 19991018 (199949) 7p
JP 3005979 B2 20000207 (200012) 9p
ADT EP 378208 A EP 1990-100474 19900111; JP 03218322 A JP 1990-5588 19900112; US 5151499 A US 1990-464077 19900112; EP 378208 B1 EP 1990-100474 19900111; DE 69011136 E DE 1990-611136 19900111, EP 1990-100474 19900111; ES 2057191 T3 EP 1990-100474 19900111; JP 09227405 A Div ex JP 1990-5588 19900112, JP 1997-70126 19900112; JP 09227406 A Div ex JP 1990-5588 19900112, JP 1997-70136 19900112; JP 2681406 B2 JP 1990-5588 19900112; JP 2965069 B2 Div ex JP 1990-5588 19900112, JP 1997-70126 19900112; JP 3005979 B2 Div ex JP 1990-5588 19900112, JP 1997-70136 19900112
FDT DE 69011136 E Based on EP 378208; ES 2057191 T3 Based on EP 378208; JP 2681406 B2 Previous Publ. JP 03218322; JP 2965069 B2 Previous Publ. JP 09227405; JP 3005979 B2 Previous Publ. JP 09227406
PRAI JP 1989-6736 19890113; JP 1989-308466 19891127

AB EP 378208 A UPAB: 19930928
Inactivation of viruses in liq. protein-contg. compsns. is effected by: (A) contacting the compsn. with a trialkylphosphate (I), drying the compsn., and heat treating the dried compsn.; or (B) contacting the compsn. with (I) in the presence of a protease inhibitor (II). Pref. (I) is tri-n-butyl phosphate (TBP) and is used in an amt. of 0.01-10%, opt. in the presence of a surfactant. Heat treatment in process (B) is effected at 30-100 deg.C for 3-200 hr.

USE/ADVANTAGE - The process are esp. applicable to plasma protein

compsns. The heat treatment step in process (A) improves inactivation of non-envelope viruses, and the presence of (II) in process (B) reduces loss of protein activity (cf. US 4540573/EP-131740).

L18 ANSWER 5 OF 5 MEDLINE
86071422 Document Number: 86071422. PubMed ID: 3934801. Inactivation of viruses in labile blood derivatives. I. Disruption of lipid-enveloped viruses by tri(n-butyl)phosphate
detergent combinations. Horowitz B; Wiebe M E; Lippin A; Stryker M H. TRANSFUSION, (1985 Nov-Dec) 25 (6) 516-22. Journal code: 0417360. ISSN: 0041-1132. Pub. country: United States. Language: English.

AB Use of the organic solvent, tri(n-butyl)
phosphate (TNBP), and detergents for the inactivation of viruses in labile blood derivatives was evaluated by addition of marker viruses (VSV, Sindbis, Sendai, EMC) to anti-hemophilic factor (AHF) concentrates. The rate of virus inactivation obtained
with TNBP plus Tween 80 was superior to that observed
with ethyl ether plus Tween 80, a condition previously shown to inactivate greater than or equal to 10(6.9) CID50 of hepatitis B and greater than or equal to 10(4) CID50 of Hutchinson strain non-A, non-B hepatitis. The AHF recovery after TNBP/Tween treatment
was greater than or equal to 90 percent. Following the reaction, TNBP could be removed from the protein by gel exclusion chromatography on Sephadex G25; however, because of its large micelle size, Tween 80 could not be removed from protein by this method. Attempts to remove Tween 80 by differential precipitation of protein were only partially successful. An alternate detergent, sodium cholate, when combined with TNBP, resulted in almost as efficient virus inactivation and an 80 percent
recovery of AHF. Because sodium cholate forms small micelles, it could be removed by Sephadex G25 chromatography. Electrophoretic examination of TNBP/cholate-treated AHF concentrates revealed few, if any, changes in protein mobility, except for plasma lipoprotein(s).

L18 ANSWER 4 OF 5 MEDLINE
88337344 Document Number: 88337344. PubMed ID: 3138794. Virus-inactivated factor VIII concentrate prevents postoperative bleeding in a patient with von Willebrand's disease. Furlan M; Lammle B; Aeberhard A; Kirste E; Sulzer I. (Central Hematology Laboratory, Inselspital, Bern, Switzerland.) TRANSFUSION, (1988 Sep-Oct) 28 (5) 489-92. Journal code: 0417360. ISSN: 0041-1132. Pub. country: United States. Language: English.

AB A patient with von Willebrand's disease underwent cholecystectomy after replacement therapy with a factor VIII concentrate that had been sterilized by treatment with tri(n-butyl)
phosphate and Tween 80. The patient received 53 units of factor VIII per kg of body weight prior to operation. In addition, a total of 280 units of factor VIII per kg was infused within 10 days after operation. This replacement regimen prevented excessive bleeding during surgery and supported normal hemostasis during the postoperative period. Analysis of the multimeric pattern and the functional assay of von Willebrand factor in factor VIII concentrates indicated that the procedures utilized for virus inactivation had no
significant deleterious effect upon the quality of von Willebrand factor molecules.

L18 ANSWER 3 OF 5 MEDLINE
92054442 Document Number: 92054442. PubMed ID: 1658928. [No HCV seroconversion in hemophilia following substitution with virus-inactivated coagulation factor VIII and IX concentrates]. Keine HCV-Serokonversion bei Hamophilen nach Substitution mit Viren-inaktivierten Gerinnungsfaktor VIII- und IX-Konzentraten. Perret B

A; Morell A; Butler-Brunner E; Burckhardt J J. (Zentrallaboratorium Blutspendedienst SRK, Bern.) SCHWEIZERISCHE MEDIZINISCHE WOCHENSCHRIFT. JOURNAL SUISSE DE MEDECINE, (1991 Nov 2) 121 (44) 1621-3. Journal code: 0404401. ISSN: 0036-7672. Pub. country: Switzerland. Language: German.

AB Since 1986 the factor VIII and IX concentrates of the Central Laboratory, Swiss Red Cross Blood Transfusion Service have been virus inactivated with tri-(n-butyl) phosphate and Tween 80. Clinical studies had shown that both preparations were well tolerated and hemostatically effective; no HIV infection was transmitted. However, safety from transmission of non-A/non-B hepatitis could not be shown since the study included no previously untreated patients. In the meantime, a laboratory test has become available which allows retrospective testing for anti-hepatitis C antibodies in frozen sera of the study patients. 5 of the 26 patients, observed during a 2-year follow-up study, had no HCV antibodies before entering the long-term trial. During this trial, each of these 5 patients substituted an average quantity of 40,200 coagulation factor units (7500-69,000) from 45 production lots. None of these 5 patients developed anti-HCV antibodies, nor did any of them show clinical signs of infection with hepatitis. This suggests that virus inactivation using solvent/detergent treatment reduces the risk of transmission of HCV.

L18 ANSWER 2 OF 5 MEDLINE

95235773 Document Number: 95235773. PubMed ID: 7719474. Purification of factor VIII and von Willebrand factor from human plasma by anion-exchange chromatography. Josic D; Schwinn H; Stadler M; Strancar A. (Octapharma Produktionsges, Wien, Austria.) JOURNAL OF CHROMATOGRAPHY. B, BIOMEDICAL APPLICATIONS, (1994 Dec 9) 662 (2) 181-90. Journal code: 9421796. ISSN: 0378-4347. Pub. country: Netherlands. Language: English.

AB Factor VIII (anti-hemophilia A factor) is isolated from human plasma. Purification is carried out by a combination of precipitation and chromatographic procedures. After precipitation, the first step in virus inactivation is achieved through the effect of a non-ionic detergent such as Tween 80, and a solvent, e.g. tri-n-butylphosphate (TnBP). By subsequent anion-exchange chromatography, a highly enriched product is isolated, consisting of a complex formed by factor VIII and von Willebrand factor (FVIII-vWF). This treatment also removes the virus-inactivating reagents to quantities in the low ppm range. The second step in virus inactivation is aimed specifically at the non-enveloped viruses and consists of pasteurization at temperatures higher than 60 degrees C for 10 h. Through the addition of stabilizers, between 80% and 90% of the initial activity of FVIII is preserved during the modified pasteurisation. Along with the possibly denatured proteins the stabilizers, such as sugars, amino acids and bivalent cations, are subsequently removed by ion-exchange chromatography. The two-fold virus inactivation, by solvent/detergent treatment and subsequent pasteurisation, allows the destruction of both lipid-enveloped and non-enveloped viruses. During the procedure FVIII is stabilized through the high content of vWF. The complex consisting of FVIII and vWF can be dissociated by adding calcium ions. Subsequently both glycoproteins from this complex are separated from one another by further anion-exchange chromatography.

L18 ANSWER 1 OF 5 MEDLINE

2000260678 Document Number: 20260678. PubMed ID: 10799053. Resistance of vaccinia virus to inactivation by solvent/detergent treatment of blood products. Roberts P. (Bio Products Laboratory, Elstree, Hertfordshire, UK.) BIOLOGICALS, (2000 Mar) 28 (1) 29-32. Journal code: 9004494. ISSN:

1045-1056. Pub. country: ENGLAND: United Kingdom. Language: English.

AB The inactivation of enveloped viruses by two different solvent/detergent combinations, i.e. tri-n-butyl phosphate (TNBP)/Triton X-100 or TNBP/ Tween 80, has been investigated using a high purity factor VIII (Replenate) and factor IX (Replenine) respectively. Treatment with TNBP/Triton X-100 rapidly inactivated all the typical enveloped viruses tested, i.e. Sindbis, semliki forest virus (SFV), herpes simplex virus type-1 (HSV-1) and vesicular stomatitis virus (VSV), by 3.7-5.8 log within 15 seconds. While virus inactivation with TNBP/Tween 80 was slower, effective inactivation of Sindbis, HSV-1, VSV and human immunodeficiency virus type-1, i.e. 4.1-->6.3 log, occurred within 30 minutes. In contrast, vaccinia virus was relatively resistant to inactivation in either of these solvent/detergent combinations. Incubation times of 10 minutes for TNBP/Triton X-100 or 6-24 hours for TNBP/Tween 80, were required to reach inactivation levels of about 4 log.